

Genetic and Environmental Vulnerabilities Underlying Adolescent Substance Use and Problem Use: General or Specific?

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Are genetic and environmental risks for adolescent substance use specific to individual substances or general across substance classes? We examined this question in 645 monozygotic twin pairs, 702 dizygotic twin pairs, 429 biological sibling pairs, and 96 adoptive (biologically unrelated) sibling pairs ascertained from community-based samples, and ranging in age from 12 to 18 years. Substance use patterns and symptoms were assessed using structured psychiatric interviews. Biometrical model fitting was carried out using age- and sex-specific thresholds for (a) repeated use and (b) problem use, defined as one or more DSM-IV symptoms of abuse or dependence. We hypothesized that problem use would be more heritable than use in adolescence, and that both genetic and environmental risks underlying tobacco, alcohol, and marijuana use and problem use would be significantly correlated. Results of univariate analyses suggested significant heritable factors for use and problem use for all substances with the exception of alcohol use. Shared environmental factors were important in all cases and special twin environmental factors were significant for tobacco use, tobacco problem use, and alcohol use. Multivariate analyses yielded significant genetic correlations between each of the substances (for both levels studied), and significant shared environmental correlations among use variables only. Our results suggest that tobacco, alcohol, and marijuana problem use are mediated by common genetic influences, but shared environmental influences may be more substance-specific for problem use.

KEY WORDS: Adolescence; alcohol; heritability; marijuana; siblings; substance use; tobacco; twins.

INTRODUCTION

Large-scale epidemiological studies have shown that by late adolescence about two-thirds of adolescents

report having used tobacco, over 80% report experience with alcohol, and approximately half-report experimentation with marijuana (CDC, 2000; Johnston *et al.*, 2001; SAMSHA, 2001). Moreover, adolescents commonly report experimentation with multiple substances rather than exhibiting substance-specific preferences. Although the development of substance use disorders (SUD) in adolescence is less prevalent, it is not rare (Kandel *et al.*, 1997; Young *et al.*, 2002), and early onset of use is a well-established risk factor for the progression from use to abuse and dependence (Bucholz *et al.*, 2000;

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Chen and Anthony, 2003; Grant and Dawson, 1998). It has been argued that this trajectory may be a by-product of an underlying pattern of disinhibitory psychopathology rather than a direct risk (McGue *et al.*, 2001).

Although the evidence for a genetic risk underlying substance use and the development of substance use problems has been converging among studies of adult twins (Kaprio *et al.*, 1987; Kendler *et al.*, 1999; McGue *et al.*, 1992; True *et al.*, 1999; Tsuang *et al.*, 1996), the extent to which adolescent substance use problems are due to genetic factors is less well understood, possibly due to the developmental nature of substance use disorders. A review of adolescent twin and adoption studies conducted through 2002 (Hopfer *et al.*, 2003) summarizes research conducted on samples in the U.S. (Maes *et al.*, 1999; McGue *et al.*, 2000; Rhee *et al.*, 2003c) and abroad (Koopmans *et al.*, 1997), which consistently show that adolescent tobacco use is under strong genetic control. In contrast, genetic influences on alcohol and marijuana use (defined as experimentation in adolescence) appear to be much less important, based on a number of large-scale adolescent twin studies (Koopmans *et al.*, 1999; Maes *et al.*, 1999; McGue *et al.*, 1996; 2000; Miles *et al.*, 2002; Rose *et al.*, 2001; Viken *et al.*, 1999). Clinically significant substance use problems, such as symptoms of abuse or dependence, have been rarely studied in adolescents. In a recent study on a subset of the current Colorado adolescent sample (Rhee *et al.*, 2003c), heritability for tobacco *problem* use (defined as one or more DSM-IV dependence symptom) was significant, but varied considerably by sex ($h^2=0.26$ for males and $h^2=0.95$ for females). McGue *et al.* (2000) reported significant genetic influences on tobacco dependence, but not on marijuana abuse/dependence diagnoses.

The search for susceptibility genes that may underlie adolescent substance use and substance use disorders can be guided by knowledge about whether general or substance-specific risks are operating. Although sparse, findings in the extant adolescent literature on the etiology of comorbidity of use across multiple substances suggest that genetic and environmental influences are common across substance classes (Han *et al.*, 1999; Koopmans *et al.*, 1999; Rhee *et al.*, 2003a). However, most family studies of the causes of comorbidity among substance use *disorders* have involved adults and have provided inconsistent conclusions regarding general versus substance-specific familial risk (Bierut *et al.*, 1998; Meller *et al.*, 1998; Merikangas *et al.*, 1998; Tsuang *et al.*, 1998).

As noted in previous research (Rhee *et al.*, 2003b), the conflicting results among the adult studies may be due, in part, to differences in the analytical methods used to examine substance-involved probands and their relatives, as well as differences in sample selection. In an adolescent sibling study involving matched clinical and control samples, Rhee *et al.* (2003a), used a biometrical model fitting approach to compare 13 alternative hypotheses of the causes of comorbidity. Results suggest that the comorbidity of alcohol and illicit drug dependence was most likely due to a single underlying familial liability.

The primary aim of the present study was to examine the genetic and environmental covariation among tobacco, alcohol, and marijuana use and problem use in order to address the question of whether or not risk factors underlying these behaviors are substance-specific. We hypothesized that we would see evidence to support a generalized risk model in our adolescent sample; that is, substantial overlap in the genetic and environmental etiology among these three commonly used substances. We take advantage of a unique study design, which combines adolescents from twin, biological sibling, and adoptive sibling samples assessed with identical structured diagnostic interviews to conduct joint analysis of these samples. This approach provides the leverage to disentangle additive genetic, non-additive genetic, shared environmental, special twin environmental, and unique environmental influences on substance use behavior.

METHODS

Participants

We examined 3744 adolescents participating in the Center for Antisocial Drug Dependence (CADD), an ongoing, multi-component, collaborative study underway at the University of Colorado. Subjects for the current study come from the twin, adoption, and family study components of the Center and were studied between 1992 and 2004. Monozygotic ($n = 645$ pairs) and dizygotic ($n = 702$ pairs) twin participants were recruited from the Colorado Twin Registry, which consists of a community-based sample of twin families residing in Colorado. A portion (28%) of the twin sample has been studied longitudinally since birth (Robinson *et al.*, 2001). The remaining 72% of the twin sample was identified through the Colorado Department of Health and 170 of 176 school districts in the state of Colorado. Only

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those who were in the adolescent age range during the study period were recruited. Non-twin participants were drawn from two community-based family samples: the Colorado Adoption Project (CAP) sample and the Colorado Adolescent Substance Abuse (ASA) family study. The CAP is an ongoing, longitudinal study of the genetic and environmental influences on behavioral, cognitive, and emotional development. Unrelated sibling pairs from adoptive families ($n = 96$ pairs) and matched community families ($n = 126$ pairs) were recruited in infancy and assessed longitudinally through early adulthood (a detailed description of the sample characteristics can be found in DeFries *et al.*, 1994). The ASA project is a study of the familial transmission of substance abuse and associated psychopathology. Patient probands and their siblings were not used for this study, but age- and ethnically matched community adolescent sibling pairs ($n = 303$) were included. The complete adolescent sample ranged in age from 12 to 18 years (mean age = 15.42; SD = 2.18) and consisted of 1799 females and 1945 males. The study protocols were reviewed and approved by the University of Colorado's Institutional Review Board and written informed assent (from minor participants) and/or consent (from adult participants or parents/guardians of minors) was obtained from each participant prior to assessment.

Assessments

Substance abuse and dependence data were obtained using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), a face-to-face structured diagnostic interview designed to be administered by non-clinician interviewers, which has been shown to be valid and reliable in both clinical and epidemiological samples (Cottler and Keating, 1990; Cottler *et al.*, 1995; Crowley *et al.*, 2001; Horton *et al.*, 2000). Although less is known about the appropriateness of the CIDI-SAM in community-based adolescent samples, an estimate of the within-pair correlation in monozygotic (MZ) twins provides a lower bound (i.e., estimate of the minimum) for reliability, because the twins are correlated because of an identical genetic makeup as well as shared home and peer environments. Thus, within-pair variation is due only to experiences unique to the individual twin and measurement error. Previous research with a large subsample ($n = 1647$) of the current MZ twins (Young *et al.*, 2002) estimated moderate to high correlations for symptoms of to-

bacco ($r = 0.59$), alcohol ($r = 0.49$), and marijuana dependence ($r = 0.37$), suggesting that the SAM is reasonably reliable in adolescent samples.

The CIDI-SAM assesses substance use patterns and DSM-IV (APA, 1994) symptoms of substance abuse and dependence for tobacco, alcohol, and eight classes of illicit drugs. Data from the tobacco, alcohol, and marijuana sections were used in the current study. In order to be asked follow-up questions regarding symptoms of abuse and dependence, subjects had to report 'repeated use', which was defined as using tobacco 'almost every day for at least a month', consuming six or more alcoholic drinks (lifetime), or using marijuana more than five times (lifetime). Thus, our use of the term 'substance use' in all subsequent analyses, tables, and discussion refers to *repeated* use as defined by the CIDI-SAM. 'Problem use' was defined as the presence of at least one DSM-IV dependence symptom for tobacco (i.e., abuse is not recognized in the DSM for tobacco), and at least one abuse or dependence symptom for alcohol and marijuana. Individuals who were unexposed to these substances (i.e., reporting never having used a substance) were coded as unaffected.

Zygoty for same-sex twin pairs was determined by a nine-item assessment of physical characteristics completed by interviewers (Nichols and Bilbro, 1966). In all cases in the current sample, MZ zygosity ratings were confirmed by twin concordance among a minimum of 11 highly informative short, tandem repeat polymorphisms. In the current sample, all discrepancies were re-genotyped and resolved.

Analyses

Descriptive statistics were obtained using SPSS (Version 12.0, 1990). For all biometrical analyses, we used Mx, a statistical modeling package developed by Neale *et al.* (1999) and freely available (<http://www.vcu.edu/mx>). Tetrachoric correlations were computed separately for MZ twins, DZ twins, biological siblings, and unrelated (adoptive) siblings. Tetrachoric correlations were computed for descriptive purposes, however, models were fit to raw binary data utilizing maximum likelihood estimation procedures operationalized in Mx. For all models tested, we assumed a normal continuous liability distribution underlying our binary assessments of substance use and problem use. Since the prevalence of substance use increases with age and, for some substances, differs by gender (Young *et al.*,

2002), age- and sex-specific thresholds were estimated and fixed to the estimated values.

A threshold approach was utilized because of the non-normality of the symptom count data in our community samples. Deviations from normality, in this case J-shaped distributions, can attenuate correlations and produce biased model parameters. The analysis of binary data, which estimates thresholds for males and females at each age separately, can be readily implemented in Mx and correctly recovers the underlying correlations and parameter estimates (Stallings *et al.*, 2001)

Cholesky (triangular) decomposition models were employed to examine the genetic and environmental structure underlying the comorbidity among tobacco, alcohol, and marijuana use and problem use. The squared, standardized loading matrices provide the proportions of variance explained by each factor (e.g., heritability) as well as the factor correlations (e.g., genetic correlations) between the substance variables. The full trivariate model included additive genetic effects (*A*), dominance genetic effects (*D*), shared environmental effects (*C*), special twin environmental effects (*T*), and unique environmental effects (*E*). The inclusion of twin, non-twin sibling, and adoptive siblings allows for the discrimination between *C* and *D* as well as *C* and *T* (see also Ehringer *et al.*, 2006; Rhee *et al.*, 2003c). A series of nested submodels, which constrain individual parameters to zero, were tested in order to ascertain the best models for explaining the covariance among these substance use phenotypes. Likelihood ratio Chi-square tests and the Akaike's Information Cri-

terion (AIC) were used to determine the significance of individual parameters and the best fitting models.

RESULTS

Prevalence Rates and Comorbidity

Table I shows the prevalence rates for substance use and problem use in males and females in each age group. As expected from previous studies, there were only small and inconsistent gender differences in prevalence. Slightly higher prevalences for males in early adolescence, which shrink by later adolescence, suggest that males have an earlier onset of substance use than girls. Although tobacco use was not common in our youngest groups, more than one in four adolescents reported using tobacco regularly in our oldest two cohorts (ages 17 and 18 years), and a majority of those using also endorsed at least one dependence symptom. Rates of alcohol use jump from 12.1 (for both males and females) to 26.2 and 35.9% (for females and males, respectively) between 14 and 15-year cohorts. For females, rates of use then increase to nearly twice that rate among 16-year olds (50.2%). Symptoms of alcohol abuse or dependence are not uncommon among male and female 16-year olds; about one in four reports at least one symptom. In our oldest cohort (18-year olds), more than one in three of the females and nearly half (47.1%) of the males report at least one symptom of alcohol abuse or dependence. Although rates of marijuana use are approximately half that of alcohol use in this adolescent sample, a higher proportion of those using marijuana also report problem use. Prevalence of use

Table I. Prevalence of Substance Use and Problem Use

Age (Years)	Sex	N	Percent reported					
			Tobacco use	Tobacco probs	Alcohol use	Alcohol probs	Marijuana use	Marijuana probs
12	Male	396	0.8	0.8	2.3	0.3	1.0	0.8
	Female	408	0.0	0.0	1.0	0.0	0.0	0.0
13	Male	174	3.4	1.7	8.0	2.3	2.3	0.6
	Female	167	0.0	0.0	6.6	2.4	2.4	1.2
14	Male	257	4.7	3.1	12.1	7.0	5.8	3.5
	Female	257	2.7	2.3	12.1	3.1	3.1	2.7
15	Male	209	12.9	11.0	35.9	15.8	14.8	11.0
	Female	191	11.0	9.4	26.2	13.6	12.6	9.9
16	Male	231	13.9	10.8	54.5	18.6	26.4	16.5
	Female	209	19.1	16.3	50.2	22.5	25.4	20.1
17	Male	421	27.3	21.6	64.6	34.9	32.5	25.4
	Female	344	27.0	22.7	63.1	29.9	29.7	24.1
18	Male	257	30.4	26.1	71.6	47.1	33.1	28.8
	Female	223	29.6	26.0	69.5	35.9	34.5	22.9

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and problem use of marijuana were nearly identical for boys and girls for each age cohort.

Phenotypic (tetrachoric) correlations among substances for use were high ranging from $r = 0.66$ for tobacco and alcohol use to $r = 0.77$ for alcohol and marijuana use. The magnitude of the phenotypic correlations for problem use was strikingly similar ranging from $r = 0.67$ for tobacco and alcohol problem use to $r = 0.77$ for tobacco and marijuana problem use.

Twin and Sibling Correlations

Sibling tetrachoric correlations for each twin and sibling group are shown in Table II for tobacco, alcohol, and marijuana use and problem use, including cross-twin/sibling, cross-substance correlations. For all comparisons, MZ twin correlations exceeded those of DZ twins, suggesting that some genetic influence is operating. With one exception, the DZ twin correlations were higher than the biological sibling correlations, raising the possibility of a special twin environmental effect. Correlations between the unrelated, adoptive siblings were small, and in most cases, non-significant, suggesting that shared, family environmental factors are exerting a minor influence on these substance related behaviors. Of note are two exceptions: the within-pair correlation for alcohol use ($r = 0.45$); and the cross-sibling correlation between alcohol use and marijuana use ($r = 0.44$).

Univariate Model Fitting

Results of the univariate model fitting are presented in Table III. For each substance category, the

best fitting model based on the Chi-square difference tests and the AIC are described. For tobacco use and problem use, the ACTE model provided the best fit to the data. Both phenotypes were moderately heritable ($a^2 = 0.47$ and 0.49 , respectively), with small, but significant shared environmental effects, and moderate, significant special twin environmental effects. In contrast, the best fitting models for alcohol use and problem use differed. A model without any significant genetic effects provided the best fit for alcohol use, including moderate shared environmental effects ($c^2 = 0.46$) and special twin environmental effects ($t^2 = 0.32$). However, results of the analysis of problem alcohol use showed strong additive genetic influences ($a^2 = 0.53$), modest shared environmental effects ($c^2 = 0.21$) and no evidence of special twin environmental effects. The best fitting models for both marijuana use and problem use included additive genetic effects ($a^2 = 0.61$ and 0.55 , respectively), shared environmental effects ($c^2 = 0.27$ and 0.24 , respectively), and unique environmental effects ($e^2 = 0.12$ and 0.21 , respectively). Sex-limitation models were fit for each of the six phenotypes, but none showed significant sex-specific genetic or environmental effects. Dominance genetic effects were also absent.

Trivariate Model Fitting

The model fitting series for the trivariate analysis of tobacco, alcohol, and marijuana use are presented in Table IV. Each submodel was tested against the full Cholesky model including variance components for A , C , T , and E . Results include the fit statistics for

Table II. Twin and Sibling Correlations for Tobacco, Alcohol, and Marijuana Use and Problem Use^a

Substance	Phenotype	MZ Twins	DZ Twins	Biological Siblings	Adoptive Siblings
Tobacco	Use	0.89 (0.81–0.94) ^b	0.67 (0.52–0.79)	0.36 (0.17–0.54)	0.06 (–0.23–0.35)
	Prob use	0.88 (0.78–0.94)	0.61 (0.43–0.75)	0.37 (0.17–0.55)	0.21 (–0.09–0.50)
Alcohol	Use	0.81 (0.72–0.87)	0.75 (0.65–0.82)	0.46 (0.30–0.60)	0.45 (0.13–0.69)
	Prob use	0.74 (0.61–0.83)	0.51 (0.34–0.65)	0.48 (0.30–0.63)	0.14 (–0.18–0.44)
Marijuana	Use	0.87 (0.79–0.93)	0.66 (0.52–0.77)	0.56 (0.40–0.69)	0.07 (–0.26–0.39)
	Prob use	0.76 (0.62–0.86)	0.62 (0.46–0.75)	0.53 (0.35–0.68)	0.03 (–0.36–0.31)
Tobacco/alcohol	Use	0.58 (0.47–0.67)	0.48 (0.36–0.60)	0.31 (0.17–0.43)	0.25 (0.03–0.45)
	Prob use	0.61 (0.50–0.71)	0.35 (0.20–0.48)	0.32 (0.18–0.45)	0.06 (–0.16–0.28)
Tobacco/marijuana	Use	0.72 (0.63–0.79)	0.52 (0.39–0.62)	0.31 (0.17–0.44)	0.12 (–0.10–0.33)
	Prob use	0.67 (0.56–0.76)	0.47 (0.33–0.59)	0.27 (0.12–0.41)	0.15 (–0.08–0.37)
Alcohol/marijuana	Use	0.67 (0.57–0.75)	0.55 (0.44–0.64)	0.39 (0.27–0.50)	0.44 (0.21–0.63)
	Prob use	0.56 (0.43–0.66)	0.42 (0.30–0.54)	0.45 (0.32–0.57)	0.11 (–0.12–0.34)

^aDSM-IV symptoms of abuse and/or dependence.

^b95% Confidence Interval.

Table III. Univariate Model Fitting Results—Best Fitting Models for Use and Problem Use

	Model	Model Fit			Parameters (95% C.I.)			Comparison to Full Model			
		χ^2	df	AIC	a^2	c^2	i^2	e^2	χ^2	df	p
Tobacco use	ACTE	2221.01	3741	-5260.99	0.47 (0.20–0.77)	0.11 (0.00–0.29)	0.32 (0.08–0.55)	0.10 (0.06–0.18)	0.00	1	1.00
Tobacco prob use	ACTE	2011.52	3741	-5470.48	0.49 (0.19–0.82)	0.15 (0.00–0.34)	0.23 (0.00–0.47)	0.13 (0.07–0.22)	0.28	1	0.60
Alcohol use	CTE	3076.26	3742	-4407.74	–(–)	0.46 (0.31–0.58)	0.32 (0.18–0.48)	0.22 (0.17–0.29)	1.20	2	0.55
Alcohol prob use	ACE	2553.40	3742	-4930.60	0.53 (0.28–0.78)	0.21 (0.01–0.40)	–(–)	0.26 (0.17–0.37)	0.07	2	0.97
Marijuana use	ACE	2472.00	3742	-5012.00	0.61 (0.41–0.81)	0.27 (0.08–0.44)	–(–)	0.12 (0.07–0.20)	1.18	2	0.55
Marijuana prob use	ACE	2178.36	3742	-5305.64	0.55 (0.29–0.80)	0.24 (0.02–0.44)	–(–)	0.21 (0.13–0.33)	0.71	2	0.70

Note: χ^2 , Chi-square; df, degrees of freedom; p , probability; AIC, Akaike Information Criterion. a^2 , proportion of variance explained by additive genetic influences; c^2 , proportion of variance explained by shared environmental influences; i^2 , proportion of variance explained by environmental influences shared only by twin pairs; e^2 , proportion of variance explained by non-shared environmental influences.

Table IV. Trivariate Model Fitting Results—Tobacco, Alcohol, and Marijuana Use

	Model Fit			Comparison to Full Model		
	-2 ln L	df	AIC	χ^2	df	p
Base model	6670.74	11211	-15751.26			
Drop A1	6676.28	11212	-15747.72	5.54	1	0.02
Drop A2	6683.10	11212	-15740.90	12.36	1	<0.01
Drop A3	6679.98	11212	-15744.02	9.24	1	<0.01
Drop C1	6689.76	11212	-15734.24	19.02	1	<0.01
Drop C2	6693.27	11212	-15730.73	22.53	1	<0.01
Drop C3	6670.94	11212	-15753.06	0.20	1	0.65
Drop E1	6679.61	11212	-15744.39	8.87	1	<0.01
Drop E2	6684.77	11212	-15739.23	14.03	1	<0.01
Drop E3	6677.56	11212	-15746.44	6.82	1	<0.01
Drop T1	6682.98	11212	-15741.02	12.24	1	<0.01
Drop T2	6678.14	11212	-15745.86	7.40	1	<0.01
Drop T3	6671.11	11212	-15752.89	0.37	1	0.54
Drop C3/T3	6671.57	11213	-15754.43	0.83	2	0.66

-2 ln L, minus twice the log-likelihood; df, degrees of freedom; AIC, Akaike Information Criterion; χ^2 , Chi-square; p , probability. Note: Parameters dropped from the base model (i.e., in the nested models labeled ‘Drop A1’, etc.) are the off-diagonal elements in each of the 4 (3 x 3) Cholesky lower triangular matrices. These elements are path coefficients for the covariances among the phenotypes, which are designated as follows: A1 = path from the first A factor to alcohol; A2 = path from the first A factor to marijuana; and A3 = path from the second A factor to marijuana. The same configuration applies to the C, E, and T factors.

each of the models tested as well as the Chi-squared difference tests for each nested comparison. The final model was one which constrained all non-significant paths to zero. Each of the final models (Figs. 1a–2b) is presented as a correlated factors model so that the proportions of variance explained by each genetic and environmental factor and the correlations among those factors (derived by multiplication of the standardized path coefficients) can be readily discerned. Figure 1a shows the final model with the corresponding (standardized) parameter estimates for the genetic and shared environmental influences on substance use. Although there were substantial heritable

influences on both tobacco use ($h^2=0.46$) and marijuana use ($h^2=0.44$), there were only trivial heritable influences on alcohol use ($h^2=0.05$). These genetic factors were only modestly (although significantly) correlated ranging from $r = 0.14$ to 0.31. The opposite patterns was observed for shared environmental influences, which were largest for alcohol use ($c^2=0.46$), and modest for both tobacco ($c^2=0.12$) and marijuana use ($c^2=0.27$). However, like the genetic factors, the shared environmental factors were only modestly overlapping.

As shown in Fig. 1b, special twin environmental factors were also retained in the best-fitting model for

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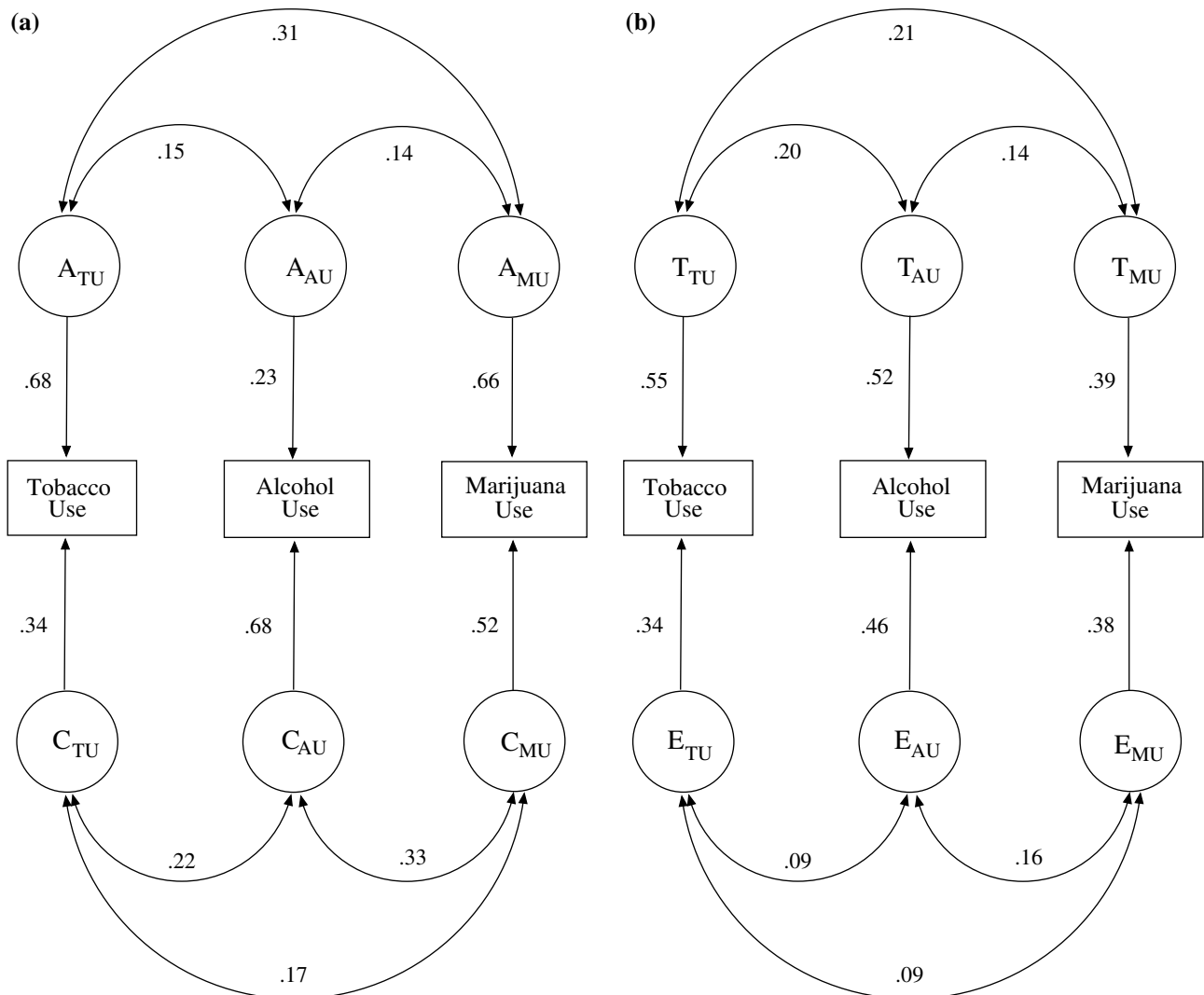


Fig. 1. (a) Results of the best fitting model for substance use: **A** represents additive genetic effects, **C** represents shared environmental effects. Path coefficients are standardized loadings which, when squared, are the proportions of variance in the phenotype explained by each factor. Loadings on the curved double-headed arrows represent correlations between two factors. Factor subscripts are as follows: TU, Tobacco Use; AU, Alcohol Use; MU, Marijuana Use. (b) Results of the best fitting model for substance use: **T** represents special twin environmental effects, **E** represents unique (to the individual) environmental effects. Path coefficients are standardized loadings which, when squared, are the proportions of variance in the phenotype explained by each factor. Loadings on the curved double-headed arrows represent correlations between two factors. Factor subscripts are as follows: TU, Tobacco Use; AU, Alcohol Use; MU, Marijuana Use.

substance use, accounting for 30, 27, and 15% of the variance in tobacco, alcohol, and marijuana, respectively. Again, there were small, but significant correlations among the latent special twin environmental factors. As expected, unique environmental factors were largely independent.

Table V presents the model series for problem tobacco use, problem alcohol use, and problem marijuana use. The final model was one in which the

common environmental and special twin environmental factors unique to marijuana were constrained to zero. As shown in Fig. 2a, the best-fitting model for problem use showed that while genetic influences were most substantial for problem alcohol ($h^2=0.70$) and problem marijuana use ($h^2=0.64$), they were slightly smaller for problem tobacco use ($h^2=0.54$). Unlike the relationship among the genetic factors for substance use, these factors were highly correlated for

Table V. Trivariate Model Fitting Results—Tobacco, Alcohol, and Marijuana Problem Use

	Model Fit			Comparison to Full Model		
	-2 ln L	df	AIC	χ^2	df	<i>p</i>
Base model	5757.66	11211	-16664.34			
Drop A1	5776.26	11212	-16647.74	18.60	1	<0.01
Drop A2	5772.10	11212	-16651.90	14.44	1	<0.01
Drop A3	5757.74	11212	-16666.26	0.08	1	0.78
Drop C1	5758.42	11212	-16665.58	0.76	1	0.38
Drop C2	5758.84	11212	-16665.16	1.18	1	0.28
Drop C3	5759.84	11212	-16664.16	2.18	1	0.14
Drop E1	5763.29	11212	-16660.71	5.63	1	0.02
Drop E2	5765.65	11212	-16658.35	7.99	1	<0.01
Drop E3	5777.10	11212	-16646.89	19.44	1	<0.01
Drop T1	5759.56	11212	-16664.44	1.90	1	0.17
Drop T2	5775.52	11212	-16648.48	17.86	1	<0.01
Drop T3	5757.93	11212	-16666.07	0.27	1	0.60
Drop ns paths	5765.13	11217	-16668.87	7.47	6	0.28

-2 ln L, minus twice the log-likelihood; df, degrees of freedom; AIC, Akaike Information Criterion; χ^2 , Chi-square; *p*, probability.

problem use ranging from $r = 0.56$ for tobacco and marijuana to $r = 0.62$ for alcohol and marijuana. For all three substances shared environmental influences were quite small and not significantly correlated with one another.

Figure 2b shows that there were moderate special twin environmental influences for problem tobacco use and problem marijuana use, but that they were minimal for problem alcohol use. With the exception of tobacco and marijuana, the special twin environmental factors were uncorrelated. As with substance use variables, the unique environmental factors were largely uncorrelated for problem use.

DISCUSSION

The aims of the present study were to examine the patterns and prevalence of adolescent substance use and problem use (defined as DSM-IV symptoms of substance use disorders) as well as investigate the genetic and environmental etiology of such use and problem use for the three most commonly used substances in adolescence: tobacco, alcohol, and marijuana. These issues were studied in a large community-based adolescent sample of MZ and DZ twins, full biological siblings and adoptive (genetically unrelated) siblings, with a total sample size of 3744 individuals ranging in age from 12 to 18 years. The study design offers a number of unique features. Our data, collected as part of the CADD, is isomorphic across a variety of family-based designs. Adolescents partici-

pating in our twin, nuclear family, and adoptive family studies are all assessed for substance use patterns and disorders with a single structured psychiatric interview. A previous study comparing the substance use patterns across these samples showed that adolescents ascertained through the CADD studies do not differ from the general population in any meaningful way, nor do they differ in substance use patterns when compared across twin, biological sibling, and adoptive sibling samples (Young *et al.*, 2002). The joint analysis of individuals with differing degrees of genetic resemblance allows for the simultaneous estimation of shared environmental and non-additive genetics effects, as well as separating shared environmental effects in all siblings raised together with those that may be specific to twins raised together (i.e., same age siblings). Additionally, applying age- and gender-specific thresholds in the model fitting analyses controls for the increasing prevalence of substance use and problem use with increasing age and any possible differences between males and females.

Some limitations of the current study should also be noted. Because our adolescent study sample was drawn from the general population, rates of diagnoses for substance use disorders are lower than we would expect to see in a clinically based sample. Consequently, we needed to apply a criterion for problem substance use (defined as meeting one or more DSM criteria for abuse or dependence) that was less stringent than that specified by the DSM-IV for a positive diagnosis. Thus, our results may not directly

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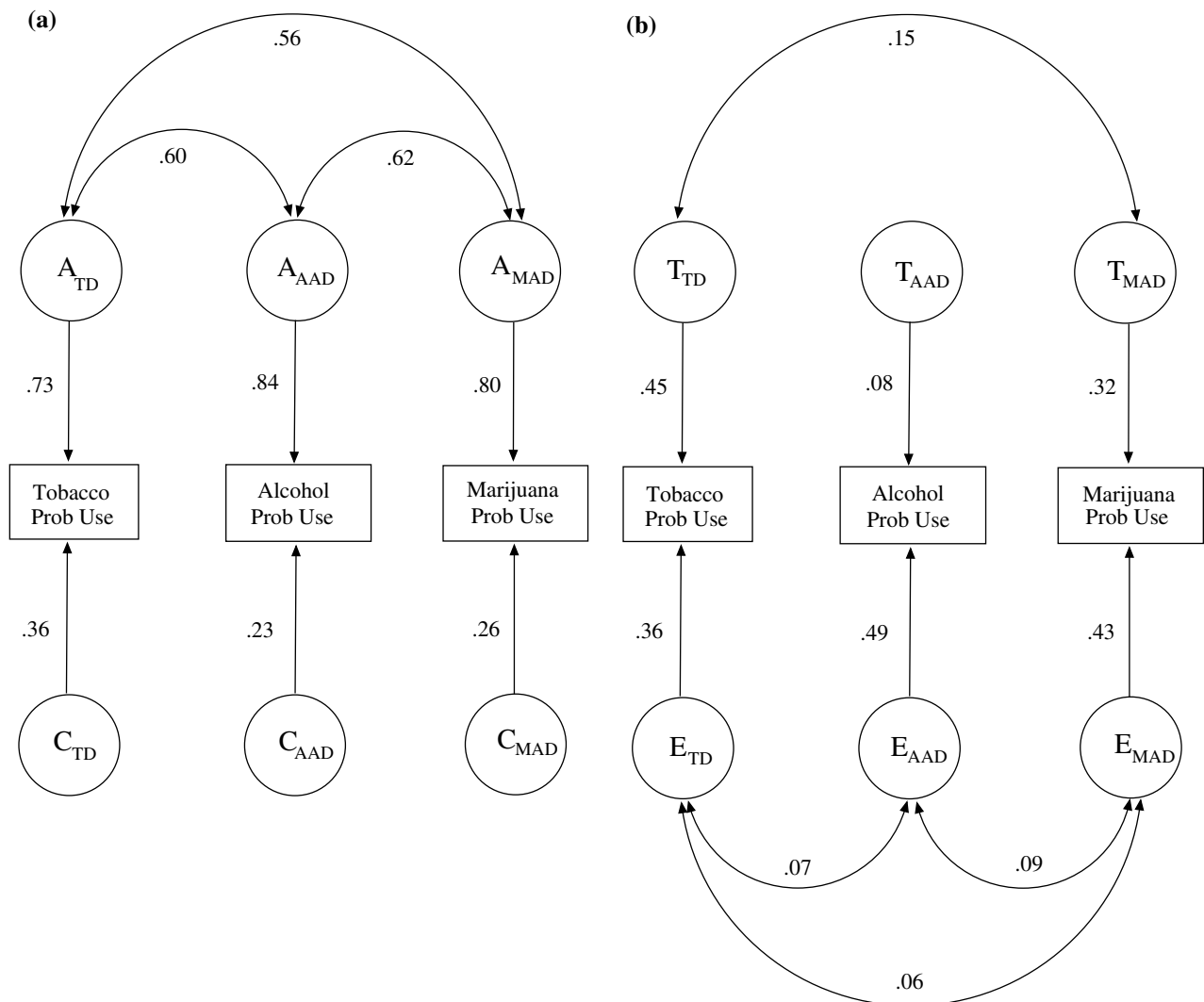


Fig. 2. (a) Results of the best fitting model for problem substance use: **A** represents additive genetic effects, **C** represents shared environmental effects. Path coefficients are standardized loadings which, when squared, are the proportions of variance in the phenotype explained by each factor. Loadings on the curved double-headed arrows represent correlations between two factors. Factor subscripts are as follows: TD, Tobacco Dependence Symptoms; AAD, Alcohol Abuse/Dependence Symptoms; MAD, Marijuana Abuse/Dependence Symptoms. (b) Results of the best fitting model for problem substance use: **T** represents special twin environmental effects, **E** represents unique (to the individual) environmental effects. Path coefficients are standardized loadings which, when squared, are the proportions of variance in the phenotype explained by each factor. Loadings on the curved double-headed arrows represent correlations between two factors. Factor subscripts are as follows: TD, Tobacco Dependence Symptoms; AAD, Alcohol Abuse/Dependence Symptoms; MAD, Marijuana Abuse/Dependence Symptoms.

generalize to more clinically severe levels of abuse or dependence.

Prevalence of Adolescent Substance Use and Problem Use

Substance use, defined by the CIDI-SAM interview as using tobacco daily for at least 1 month, drinking alcohol more than five times, and using

marijuana more than 5 times, was fairly common in our sample. The majority of adolescents who reported using tobacco at this level also reported one or more symptom of DSM-IV defined dependence, underscoring the addictive nature of nicotine. In contrast, the development of problem alcohol use was much less prevalent than alcohol use. For most age groups, fewer than half of those individuals reporting repeated use also reported problem use. For mari-

juana, the ratio of symptoms-to-use rates was intermediate to those for tobacco and alcohol. The high comorbidity among the three substances studied confirms our previous work in adolescent samples (Rhee *et al.*, 2003a; Young *et al.*, 2002). Within-person correlations among the substances were substantial for both use and problem use ranging from $r = 0.66$ to 0.78 , suggesting that adolescent substance users tend to be polysubstance users, and typically have problems with all of the substances being used.

Etiology of Adolescent Substance Use and Problem Use

The familial nature of adolescent substance use was highlighted by the significant sibling correlations for all substances in all biologically related groups; sibling correlations for adoptive siblings were modest. Results of the univariate threshold models demonstrated that the sibling resemblance observed was, with one exception (i.e., alcohol use), largely genetic in nature. Shared environmental influences varied by substance, showing a modest influence on tobacco use and problem use, but substantial influence on alcohol use, accounting for nearly half of the phenotypic variance. Although the aggregation of data from twin, full biological, and adoptive siblings allowed us to simultaneously estimate shared environmental factors and dominance genetic factors (i.e., not possible with twin samples alone), we found no evidence for dominance genetic effects for any of the substance use measures.

These results are largely consistent with previous studies of adolescent substance use in genetically informative samples. A review of twin and adoption studies conducted through 2002 (Hopfer *et al.*, 2003) concluded that individual differences in adolescent tobacco use are under strong genetic control (Koopmans *et al.*, 1997; Maes *et al.*, 1999; McGue *et al.*, 2000). More recently, a study by Rhee *et al.* (2003c), which utilized a large subset of the current Colorado sample, estimated heritability for tobacco problem use 26% for males and 95% for females. Although there was no evidence for sex-specific genetic effects in the current sample, there were substantial special twin environmental effects for tobacco use and problem use. It is possible that twins share a uniquely similar environment, in part because, unlike other biological siblings, they are the same age. Our support for a special twin environmental effect is consistent with a previous report that twin closeness

is associated with concordance for smoking initiation (Kendler and Gardner, 1998); however, the earlier study did not find the same association with nicotine dependence.

In contrast to findings for tobacco, genetic influences on alcohol use (defined as experimentation in adolescence) appear to be much less important. Similar findings have been reported across a number of large-scale adolescent twin studies, despite broad cultural differences (Koopmans *et al.*, 1999; McGue *et al.*, 1996; Rose *et al.*, 2001; Viken *et al.*, 1999) and variability in how drinking was defined (e.g., initiation, intoxication, frequency of drinking). We also found evidence for special twin environmental influences on alcohol use. A similar result was reported by Pennikilampi-Kerola *et al.* (2005), in a study which showed that twin closeness modulated genetic effects on drinking habits, especially in adolescence. Although there is a dearth of published research on alcohol use disorders in adolescent populations, previous studies have shown that, once drinking has initiated, individual differences in frequency and quantity of drinking are strongly influenced by genetic factors (Rose, 1998). Results in our adolescent sample suggest that problem alcohol use is moderately heritable ($h^2=0.53$), and less influenced by shared environmental factors ($c^2=0.21$).

Results of the analysis of marijuana use differ somewhat from previous adolescence twin studies, which have typically reported modest heritabilities and substantial shared environmental factors (Maes *et al.*, 1999; McGue *et al.*, 2000; Miles *et al.*, 2001, 2002). In the current sample, we found evidence for strong genetic influences and weaker common environmental factors for both marijuana use and problem marijuana use. These differences may be due, in part, to the fact that the current study samples included (non-twin) biological siblings, who showed within-family correlations slightly lower than those for DZ twins despite having the same level of genetic resemblance.

More central to the aims of the current study are the findings of our multivariate model fitting analyses, which examine the degree of overlap among the genetic and environmental factors influencing adolescent substance use and problem use. With respect to use, comorbidity among tobacco, alcohol, and marijuana in adolescence appears to be driven both by common genetic factors as well as common family environmental factors and special twin environmental factors. The strongest genetic overlap ($r_a=0.31$) and weakest family environmental overlap ($r_c=0.17$)

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was seen between tobacco and marijuana use. Other correlations among the factors differed minimally across pairs of substances. Only a few previous studies have examined the degree to which a common set of genetic or environmental factors underlie the risk for adolescent substance use. Koopmans *et al.* (1997) found no evidence of genetic overlap between risk for smoking and alcohol use in Dutch adolescent twins (under the age 17), but significant genetic correlations in young adults (ranging in age from 17 to 25 years). Conversely, Han *et al.* (1999) reported that a single common genetic factor could explain the risk underlying tobacco, alcohol, and other drugs of abuse in adolescent twins participating in the Minnesota Twin Family Study. Similarly, Rhee *et al.* (2003a), tested 13 alternative hypotheses of the causes of comorbidity among substance use variables in biological siblings and demonstrated that the comorbidity of alcohol and illicit drug dependence was most likely due to a single underlying familial liability, which is consistent with the findings in the current study.

In contrast to our findings for substance use, the genetic correlations among all problem use measures were consistently strong, ranging from $r_a=0.56$ to 0.62. The correlations among the family environmental factors were non-significant, but problem tobacco use and problem marijuana use shared common twin environmental factors. Thus, as previous studies have suggested, not only are more severe phenotypes for substance use more heritable, but they are also driven by common genetic risk factors. We could find no previous published studies of the genetic and environmental overlap among substance use disorders (i.e., diagnoses) or symptoms of the disorders in adolescent samples. However, two previous adult twin studies have supported the hypothesis that the liability to marijuana and other illicit drug use results from a common set of genetic and shared environmental risk factors (Karkowski *et al.*, 2000; Kendler *et al.*, 2003a, b).

One limitation of the separate analysis of use and problem use is that these categories are not independent. That is, a portion of individuals who are in the repeated use category are also in the problem use category. A multilevel analysis, which places individuals in mutually exclusive categories (no use, repeated use without problems, problem use) could result in somewhat different parameter estimates. It is also worth restating that our criterion for problem substance use did not require a certain constellation of abuse or dependence symptoms, nor did it reflect a

high level of severity in many cases. Thus, adolescents crossing our problem use threshold may be rather heterogeneous in their symptomatology. For example, an adolescent using both tobacco and alcohol may report considerable dependence on nicotine, but more symptoms of abuse for alcohol. Hence, there may be substance-specific genetic variance (recalling that the genetic correlations were less than 1.0), influencing abuse or dependence symptoms that are idiosyncratic to individual substances (e.g., reflecting sensitivity to the particular pharmacological characteristics of the substance).

By and large, our results add to previous evidence in support of the hypothesis that the genetic vulnerability for the development of adolescent substance use and problem use is not substance-specific, but operates in a more general way across a variety of psychoactive substance classes. If true, this conclusion could offer guidance for research involved in the search for susceptibility loci for substance use disorders. In particular, these findings suggest that in adolescence the genetic variants may have pleiotropic effects, underlying a spectrum of disorders, rather than more compound-specific effects.

Our findings could prove useful for those involved in the assessment or treatment of adolescents referred with substance use problems. Adolescents who have progressed from experimentation with substances to the development of signs of abuse or dependence may possess a broad biological susceptibility that may not respond well to substance-specific treatments such as those developed for adults with substance use disorders (e.g., nicotine patches, antabuse, Alcoholics Anonymous, methadone maintenance, etc.). These youth may benefit more from interventions that target a proclivity for indiscriminate psychoactive substance use, which may also be associated with comorbid psychopathology.

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